A Multi-State, Allosterically-Regulated Molecular Receptor With Switchable Selectivity

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1. Introduction

1.1 Allosteric Effect — Switchable Binding Activity to Substrate

Allosteric effect — The binding activity between an enzyme and its substrate could be regulated when another small molecule (effector) binds to the regulation site.

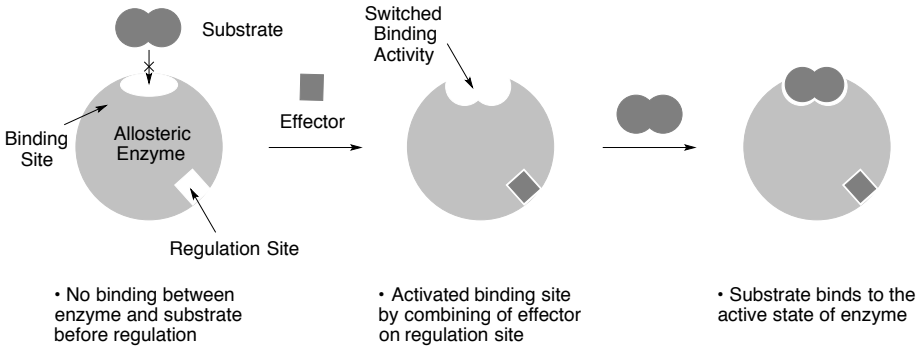


Figure 1. Allosteric Regulation Process in Biological Enzymes

1.2 Two Types of Regulation Mechanism in Allosteric Enzymes *(Figure 2.)*

A. physical access to binding site (active/inactive)

B. chemical affinity of binding site (multiple active states)

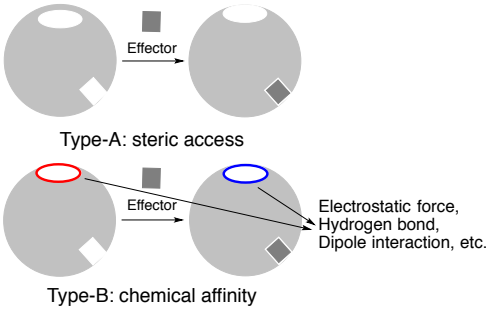


Figure 2. Two Regulation Types

1.3 Artificial Allosteric Systems

- Wide application in phase transfer catalysis, drug delivery, sensing.
- Abiotic type-**A** regulation have been achieved with transition metal coordination center regulation systems. (***Figure 3.***)
- However, switching between multiple active states (type-**B**) remains challenging — modification of chemical affinity without changing steric profile is difficult.

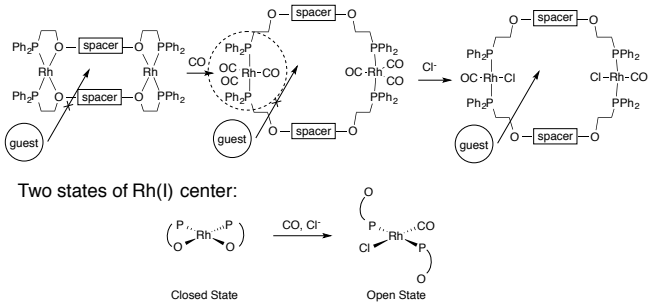


Figure 3. Type-A Coordination Regulated System[1]

1.4 This Work: Combination of Two Regulation Types, Switchable Active States

- Design and synthesis of a Pt center regulated receptor **1**
- Regulation between inactive state **1** and two different active states **2** and **3** by anion effectors Cl^- and CN^- by combination of two regulation mechanisms.
- Selective binding of two sterically similar guest molecules N-Methylpyridinium (**5**) and Pyridine N-oxide (**6**) by two active states **3** and **2**, respectively. (***Figure 4.***)

2. Results and Discussion

2.1 System Design

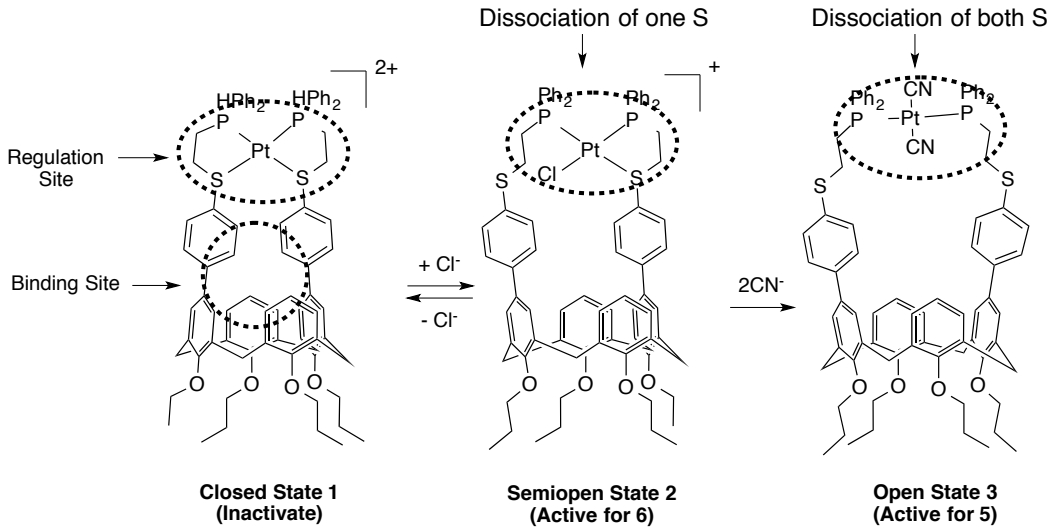


Figure 4. Allosteric Regulation between inactive and Different Active States by Anion Effectors

2.1.1 Regulation Site — Stepwise Ligand Exchange on Pt(II) (*Figure 5.*)

- Step 1: Similar coordination strength between S-Pt and Cl-Pt[2] —dissociation of one sulfur ligand and therefore formation of semi-open state **2**
- Step 2: Strong coordination ability and trans effect of CN^- — substitution of both sulfur ligands and cis/trans switch and therefore formation of fully open state **3**

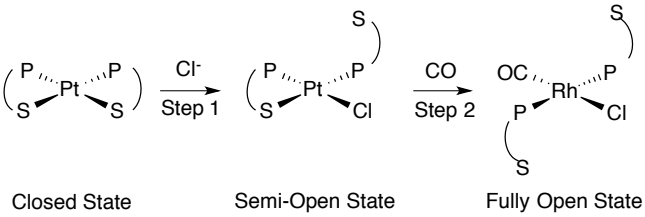
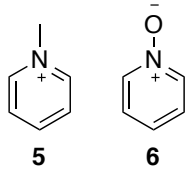


Figure 5. Three States of Pt(II)-Centered Coordination[2]

2.1.2 Binding Site (*Figure 4.*)

- *Calix[4]arene* — Easily tuned conformation by modifications of upper and lower rims;
- *Aromatic spacer* — High affinity for small aromatic guests; Rigid backbone capable of transferring modification from Pt center to calixarene.

2.1.3 Model Guest Molecules 5 and 6



5 **6**

- Aromatic ring capable of π-π stacking
- Similar size
- Different electrostatic property enabling selective binding

2.2 NMR Titration — Selective Formation of Inclusion Complexes

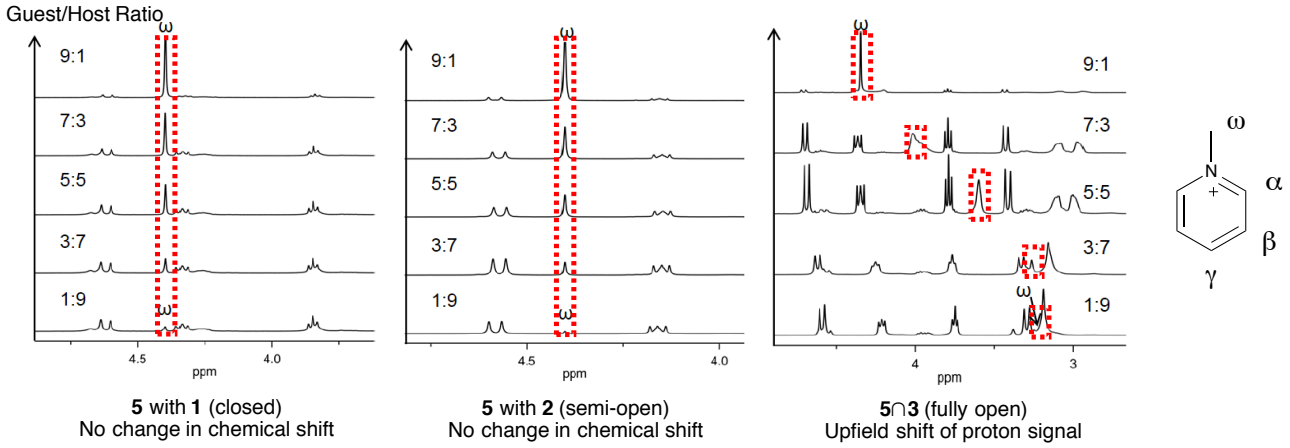


Figure 6. NMR Trace of Guest **5** with Three States of Receptor

Upfield shift of ω-protons in **5** (***Figure 6.***) suggests the inclusion of the whole molecule into host cavity. The shift is only observed with full open state **3**, proving the selective binding of **5** by **3**.

Similar phenomenon is observed between **2** and **6.**

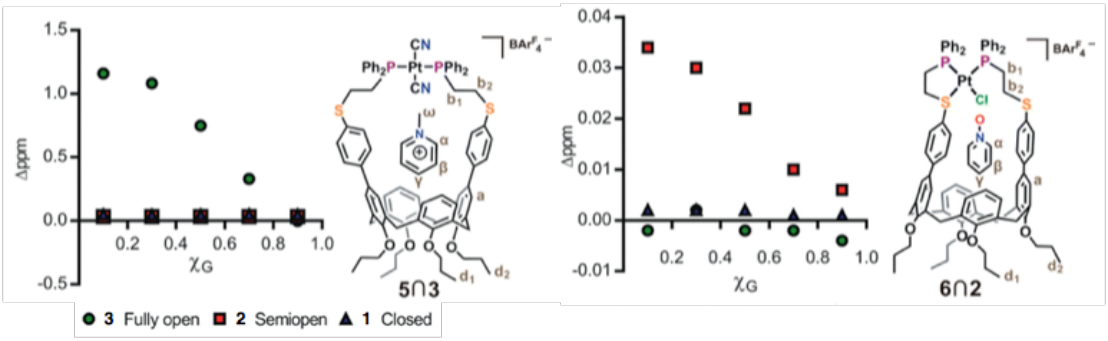


Figure 7. Comparison of NMR Signal Shift in Titration of **5** or **6** into Receptors **1-3**

Comparison of the NMR signal shifts when titrating guest molecules into different states of receptor (***Figure 7.***) indicates the selective formation of **5∩3** and **6∩2.**

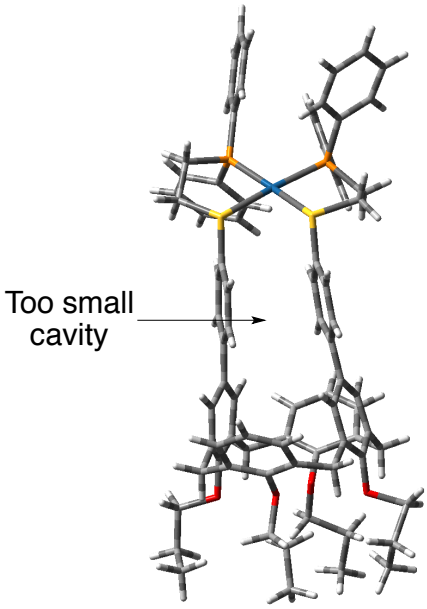


Figure 8. Solid-State Structure of State **1**

2.3 Mechanism Interpretation — Crystal Strucure & Computational

2.3.1 Inactive Closed State 1 *(Physical inaccess)*

Neither **5** nor **6** forms inclusion complex with receptor **1**.

In solid state structure of **1** (***Figure 8***), the π–π interaction between two aromatic spacers blocks the guest molecules from entering the cavity.

2.3.2 Active Semi-Open State 2 *(Chemical affinity)*

Only guest **6** is binded to receptor **2.**

✓ Interactions in **6∩2** (***Figure 9.***)

1) π–π stacking — π in **6** with π∗ in **2**
2) Dipole-dipole — anti-parallel alignment of dipoles
3) n-σ* interaction — lone pair of O (**6**) with Pt(II) and C–H σ∗ orbital (ethyl part of P,S ligand)

× **5** with **2**

Both **5** and **2** are positively charged. The electrostatic repulsion prevents the inclusion.

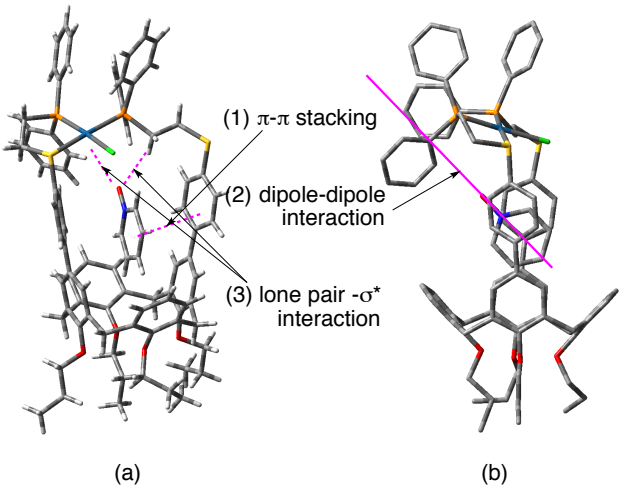


Figure 9. (a) Solid-State Structure of 6∩2; (b) Side View of 6∩2

2.3.3 Active Fully Open State 3 *(Chemical affinity)*

Only cationic guest **5** is binded to receptor **3.**

✓ Interactions in **5∩3**

π–π stacking — bonding orbital in **3** with antibonding orbital in **5**

× **6** with **3**

According to the molecular orbitals involved in π–π stackings of **6∩2** and **5∩3**, the related MOs in **6** and **3** are mismatched.

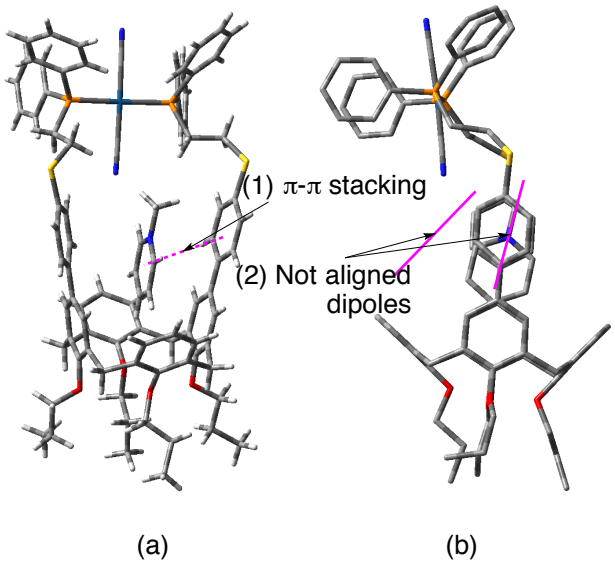


Figure 10. (a) Solid-State Structure of 5∩3; (b) Side View of 5∩3

Switch between inactive and different active states by combinatory regulation of physical accee (type-A) and chemical affinity (type-B).

3. Conclusion

✓ Design and synthesis of a Pt(II) coordination regulated molecular receptor

✓ Switch between *on/off states* as well as *multiple active states*.

✓ Alteration of binding selectivity controlled by *cavity size* and *electrostatic, dipole property, MO energy*.

4. Referrence

i. Kawabara, J.; Stern, C. L.; Mirkin, C. A. *J. Am. Chem. Soc.*, **2007**, *129*, 10074.

ii. (a) Anderson, G. K.; Kumar, R. *Inorg. Chem.* **1984**, *23*, 4064. (b) Kennedy, R. D.; Machan, C. W.; McGuirk, C. M.; Rosen, M. S.; Stern, C. L.; Sarjeant, A. A.; Mirkin, C. A. *Inorg. Chem.* **2013**, *52*, 5876.